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Pharmacokinetics of Mycophenolic Acid in Patients with Lupus Nephritis

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Abstract

Lupus nephritis is associated with urinary protein excretion, hypoalbuminemia, and renal function declines, which may impact the pharmacokinetics (PK) of mycophenolic acid (MPA).

The primary study objective was to evaluate and describe the PK of MPA and its glucuronide (MPAG) in lupus nephritis. Secondary objectives were to determine the single and/or multiple effects of clinical parameters (urinary protein excretion, serum albumin, and creatinine clearance) and demographic variables (age, race, and gender) on total and unbound MPA and MPAG PK.

Plasma and urine were collected for 24-hours and assayed by HPLC with UV detection. Noncompartmental PK analysis was performed using WinNonlin v4.1. Statistics included descriptive analyses, urivariate and multiple regression tests, and T-test or nonparametric equivalent.

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Time to maximal concentration (0.5 to 8 hrs) was variable. Unbound MPA was 2.6±1.9% and oral clearance (Cl/F 343 ± 200 mL/min) was ~ 2-fold higher than previously reported. Multiple regression showed MPA Cl/F was predicted by creatinine clearance (Clcr) and serum albumin (MPA lnCl/F = 5.358 + 0.0092 (Clcr) − 0.078 (ranked albumin), R^2 51.1%, p = 0.0195). UP:Cr ≥ 1 g/d had lower trough and area under the curve (AUC_{0-12}) and higher Cl/F versus UP:Cr < 1 g/d. Serum albumin < 4 g/dL had higher MPA Cl unbound and MPAG Clr_{0-12} versus serum albumin ≥ 4g/dL. Recycling AUC (AUC_{6-12}) and equally gender and age predicted renal clearance of MPAG.

Clcr and serum albumin were identified as primary contributors to MPA exposure and should be considered when evaluating dosages. The results of future studies should clarify the interactions of other variables on drug exposure and treatment responses. Clinicians need to be mindful of clinical changes that occur throughout the course of lupus nephritis in order to maintain efficacy and reduce toxicity from MPA therapy.

Keywords

lupus nephritis; mycophenolic acid; pharmacokinetics; individualized therapy

Introduction

Mycophenolic acid (MPA) has been used as an immunosuppressant agent to prevent renal transplant rejection since 1995. As there is inherent variability in mycophenolic acid pharmacokinetics within transplant patients, several researchers have sought to describe mycophenolic acid variations that occur from the early post-transplant period to several months after transplant.[1-3] More recently, it has been suggested that therapeutic plasma monitoring of mycophenolic acid may help to improve immunosuppressive outcomes. [4] Area under the plasma concentration time curve from 0 to 12 hours (AUC_{0-12}) of 30 to 60 mcg h/L and trough plasma concentrations (Ctr) of 1 to 3.5 mcg/mL are suggested as targets for combination immunosuppressive therapy (MPA plus cyclosporine and steroids) in renal and heart transplant patients. [4-5] These concentrations are based on high performance liquid chromatography (HPLC) assays. Target ranges for MPA in single or double agent therapies or for use in autoimmune diseases have not been established.

Since 1999, mycophenolic acid therapy has been evaluated for efficacy in patients with lupus nephritis. [6-9] Similar to renal transplant recipients, glomerular disease patients often have diminished renal function manifest as reductions in glomerular filtration rate (Clcr). However, glomerular disease patients also commonly have protein in the urine and alterations in serum albumin. Both urinary protein and decreased serum albumin (in addition to altered Clcr) conceivably could lead to pharmacokinetic alterations of highly protein bound drugs such as MPA in patients with glomuerulonephritis. Hence, a comprehensive evaluation of total and free MPA pharmacokinetics in lupus nephritis patients on stable therapy is warranted. Analyses of the impact of alterations in urinary protein, serum albumin, and Clcr on pharmacokinetics could provide patient-specific factors that may be important for individualized dosing.

The primary purpose of this study was to evaluate the total and free pharmacokinetics of MPA and its phenolic O-glucuronide (MPAG) in patients with lupus nephritis. The secondary objectives were to determine the effects of clinical parameters (urinary protein excretion (UP:Cr), serum albumin, and Clcr) and demographic variables (age, race, gender) on total and unbound MPA and MPAG pharmacokinetics.

Methods

Patients

Patients with biopsy confirmed lupus nephritis receiving maintenance therapy with MPA were evaluated for study enrollment. Patients were required to be on a stable MPA dose for at least two weeks. Concomitant therapy with other immunosuppressants was allowed and recorded. Patients were fasting at study initiation and were fed a standard diet in the research unit throughout the study period. The following clinical data was measured at the time of the study or abstracted from the medical record: Clcr, UP:Cr, serum albumin, and serum creatinine. The study and consent form was approved by the University's Institutional Review Board and patient consent was required prior to participation.

Pharmacokinetic Study

Patients were admitted to the General Clinical Research Unit (GCRC) to participate in a 24-hour inpatient stay for pharmacokinetic analysis. Baseline blood was drawn for a trough plasma concentration. The patients were then instructed to take their morning oral dose of MPA. Additional plasma samples (7.5 mL) were obtained at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours. Urine was collected during the following intervals: 0-6, 6-12, and 12-24 hours into acidified (15 mL 6 N HCl) collection containers. Heparinized blood samples were immediately centrifuged for 10 minutes at 4C, plasma transferred to plastic screw top tubes and stored at -80 until assay. Urine volume for each collection time period was recorded, and 2 mL aliquots were stored at -80C until assay. Unbound plasma fraction was determined by filtration via a Centrifree® Micropartition device (Millipore, Ireland) with a filter cut-point of 30,000 daltons. Temperature and centrifugation conditions were optimized to enable filtration of 10% of the total plasma volume. The unbound fraction was assessed at the time point corresponding to the Cmax and evaluated in spiked plasma separately. The unbound concentrations were then calculated as unbound fraction multiplied by total concentration. Linearity of binding throughout the evaluated concentration ranges was assumed. Samples were assayed by HPLC using a variation on the methods of Wiwattanawongsa, et al [10], using methanol-formic acid 0.1% isocratic mobile phase (52:48) at a flow rate of 1.0 mL/min, suprofen as the internal standard, and UV detection at 250 nm. The HPLC system consisted of a Hewlett-Packard series 1050 pump/injector, Hewlett-Packard Series 1050 UV detector, and Axxiom ODS column (150 × 4.6 mm I.D., 5 micrometers). Plasma and urine standard curves for MPA were linear over the range of 0.2-200 mcg/mL and 1-50 mcg/mL, respectively. Plasma and urine standard curves for MPAG were linear over the range of 1-50 mcg/mL and 5-1500 mcg/mL, respectively. MPAG concentrations were represented in terms of MPA-equivalents by multiplying each MPAG concentration by 0.646 (molecular mass of MPA to MPAG) and reported in mcg/mL. The amount of MPA available from a dose of the prodrug was estimated as 72% of the dose (molecular mass of MPA to MPA mofetil). This calculation was used to determine the amount of drug excreted in the urine in reference to the dose of MPA actually administered from mycophenolate mofetil.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic analysis of total and unbound MPA and MPAG was conducted using WinNonlin v4.1 (Pharsight, Mountain View CA) linear up-log down for AUC determination. The following parameters were reported: concentration maximum (Cmax), time to maximum concentration (Tmax), concentration trough (Ctr) at 12 and 24 hours, area under the plasma concentration time curve from 0-12 hours (AUC_{0-12}), oral clearance (Cl/F), renal clearance (Clr), and mean residence time (MRT). For the purpose of pharmacokinetic evaluations we made the assumption that F = 1, since others have reported bioavailability of close to 1. [2] AUC_{12-24} and AUC_{6-12} were calculated. The AUC_{6-12} was used to estimate entero-hepatic recycling as performed by others. [11-12] Urine analysis was performed by

multiplying the concentration by volume for each collection period (0-6, 6-12, and 12-24). Amount excreted in the urine (Ae) was computed for the 0-12 hour time frame by adding the Ae for the first two collection intervals. Clr for the 0-12 hour time frame was calculated by Ae_{0-12}/AUC_{0-12}.

Statistics

Descriptive analyses for pharmacokinetic parameters, demographic variables and laboratories included means, standard deviations, and medians as appropriate. Univariate assessments of the key clinical characteristics (serum albumin, UP:Cr, Clcr, age, race, gender, steroid dose) versus each pharmacokinetic parameter of interest (MPA Cl/F, MPA Clr, MPA unbound clearance (Clunb), MPAG Clr, MPA AUC_{0-12}, MPA AUC_{6-12}, MPAG AUC_{0-12}) were assessed by Spearman Rank correlations. The correlations and resultant p values from the univariate assessments were analyzed for possible inclusion into a multiple regression model for prediction of the pharmacokinetic parameters of interest. All data that failed normality testing were transformed by various functions to ensure normality was attained. Model building consisted of using multiple regression analysis with forward addition of variables as well as backward elimination, noting any significant changes in coefficients of the primary predictors as well as the R^2 and p value resulting from the various models. The final model was selected based on significance of each variable on predicting the dependent variables in the model as well as the overall R^2. Race (white and non-white) and gender (female and male) were coded as 1 and 2, respectively.

Comparisons between clinical groups based on urinary protein excretion (< 1 g/day vs ≥ 1 g/day), serum albumin (< 4 g/dL vs ≥ 4 g/dL), age (< 40 yrs vs ≥ 40 yrs), race (white vs nonwhite), and gender (female vs male) were analyzed by the nonparametric Mann Whitney Test. Upon review of our data, it was not possible to compare Clcr groups as there was no meaningful cut-point value for evaluation.

Results

A total of 18 biopsy-confirmed lupus nephritis patients completed 21 full twenty-four hour MPA/MPAG pharmacokinetic evaluations. We report the results for the 18 discrete patients. The patient demographic composition included age 36 ± 9 years, 83% female, 60% non-Caucasian, and weight 82.3 ± 22 kg. The non-Caucasian patients consisted of 7 African American, 2 Asian, and 2 Native American. All patients were receiving the mycophenolate mofetil prodrug of MPA (Cellcept®, Roche). The average MPA daily dose was 1860 ± 764 mg and this was represented by twice daily dosing in all but one patient who received 1000 mg three times daily. The distribution of doses given twice daily were 500 mg (n = 6), 750 mg (n = 1), 1000 mg (n = 7), and 1500 mg (n = 4). Clcr was used as the assessment of GFR in this study. [13] The mean (± standard deviation) clinical laboratory results at baseline were serum creatinine 1.1 ± 0.8 mg/dL, UP:Cr 1.3 ± 2.2, Clcr 114 ± 49 mL/min, and serum albumin 3.9 ± 0.4 g/dL. Fifty percent (n = 9) of patients were receiving concomitant glucocorticoids, with a mean ± SD daily dose of 11.4 ± 8.9. No other immunosuppressants were prescribed. Two patients were prescribed oral contraceptives.

MPA Pharmacokinetics

A representative concentration vs time profile for steady state MPA and MPAG concentrations in our lupus nephritis patients is presented in Figure 1. The mean (± standard deviation) pharmacokinetic parameters for patients with lupus nephritis are provided in Table 1. In order to eliminate differences secondary to body size, the oral clearance (Cl/F) data was adjusted to a 70 kg patient based on a scaling method that uses a power of 0.75. [14] The Cl/F of 343 ± 200 mL/min suggests that MPA is a moderate extraction ratio drug whose metabolism would be

impacted by changes in unbound fraction. While the mean percentage of free MPA was 2.6 ± 1.9, five patients (28%) had free MPA percentages that were greater (range 2.9 to 6.3%). The mean MPA area under the plasma concentration time curve (AUC_{0-12}) in our lupus patients was above the range of 30 to 60 mg hr/L recommended in the first six months post renal transplant, [15] with 39% of patients exceeding and 22% failing to achieve this range. Examination of the AUC_{6-12} to the AUC_{0-12} suggested that recycling accounted for 37% (± 16%) of the AUC reflected from the first daily dosing interval.

The mean MPA trough (Ctr) at 12 hours exceeded the range of 1.0 to 3.5 mcg/mL that is recommended in transplant patients [15], with 28% of patients below and 33% above this target, respectively. The Ctr that resulted after the first 12 hours was ~20% less than the Ctr following the second dosing interval, however the difference was not significant. The time to maximal concentration (Tmax) varied in the range of 0.5 to 8 hours and would not have been appreciated in shortened sampling schemes. A three hour AUC profile would have under-represented exposure over the dosing interval.

As suggested previously [2], the clearance of MPA is primarily the result of systemic metabolism to MPAG. The renal clearance (Clr) for MPA represented ~ 1% of the Cl/F. The Clr of nonmetabolized MPA was 1.8 ± 1.4 mL/min, which was ~ 2% of the Clcr in the evaluated patients. The kidneys contributed to the excretion of 1% of the total MPA dose, assuming all MPAG formed was via the liver. The amount of MPA in the urine over the 0-12 hour interval (4.8 ± 3.3 mg) was ~25% less than the amount in the 12-24 hour interval (6.5 ± 9.1 mg), despite the dosages being consistent, but this was not significant. The Clr was similar between the 0-12 hour and 12-24 hour dosing intervals.

MPAG Pharmacokinetics

The MPAG pharmacokinetic results are presented in Table 1. The MPAG Ctr after the first 12 hours was ~15% less than the Ctr following the second dosing interval. A calculated AUC ratio of MPAG to MPA resulted in a metabolic ratio (MR) of 7.1 ± 4.8.

The renal clearance of MPAG was 53.5 ± 52.3 mL/min, which was 44% of the Clcr. The kidneys contributed to the elimination of 96% of the total MPA dose through excretion of the metabolite, MPAG. Hence, the kidneys were responsible for eliminating ~97% of the total dose of MPA. The remaining MPA was likely eliminated secondary to excretion of the acyl MPAG metabolite by the kidneys (not measured) as well as by biliary secretion of MPAG that is not recycled. The amount of MPAG in the urine over the 0-12 hour interval (565 ± 310 mg) was ~28% more than the amount in the 12-24 hour interval (441 ± 341 mg), despite the dosages being consistent. The Clr was similar between the 0-12 hour and 12-24 hour dosing intervals.

Unbound Pharmacokinetics

Our patient data showed that 2.5% and 9.3% of MPA and MPAG, respectively, were unbound in the plasma. Since the unbound MPAG was less than that reported previously [16], we reviewed our data with normal plasma that was spiked with MPA and MPAG either alone or in combination. The blank plasma that was spiked separately demonstrated similar percentages to that found in our patient data. The combination drug and metabolite spiked plasma showed an increase in unbound percentage of 4% and 11% for MPA and MPAG, respectively, suggesting competitive binding to albumin as reported previously.

Since the normal percentage of unbound MPA is ~2%, if one aims for a total Ctr of 1.0 to 3.5 mcg/mL then an unbound target would be 0.02 to 0.07 mcg/mL. Likewise, if suggested total AUC goals are 30 to 60 mcg h/mL, then unbound AUC goals would be 0.6 to 1.2 mcg h/mL. Our data showed mean unbound Ctr levels (0.1 mcg/mL at 12 and 0.13 mcg/mL at 24 hours)

that were greater than suggested, with 44.4% of patients within the range. With regard to unbound AUC, the mean exposure was greater than the upper range of 1.2 mcg h/mL in 33% of our lupus patients.

Regression Results

Multiple regression was performed to determine which clinical factor (UP:Cr, Clcr, serum albumin, age, race, gender, steroid dose) had the most effect on pharmacokinetic parameters for MPA (Clr, Cl/F, AUC $_{0\text{-}12}$, AUC $_{6\text{-}12}$) and MPAG (Clr, AUC $_{0\text{-}12}$). MPAG clearance parameters were included as increased MPAG may result in enhanced recycling and subsequent increases in MPA exposure. Models were constructed by forward selection and backward elimination schemes employing the pharmacokinetic parameter as the Y factor and clinical variables as the X factors. $AUC_{6\text{-}12}$ was also included as an X factor when Clr variables were assessed. The Clcr and serum albumin were the two clinical parameters contributing to MPA Cl/F. Ln MPA Cl/F = 5.3585 + 0.0092 (Clcr) − 0.0776 (ranked serum albumin), R^2 51.1%, p = 0.0195; Clcr p = 0.0265, serum albumin p = 0.0586. The regression equation for MPA AUC $_{0\text{-}12}$ demonstrated similar results, which is expected given the reciprocal relationship between Cl/F and AUC $_{0\text{-}12}$. For the MPAG Clr analyses, the AUC $_{6\text{-}12}$ was consistent in models that controlled for either gender or age. These two models were: 1) Ln MPAG Clr = 6.6009 − 1.3519 (gender) − 0.5257 (ln AUC $_{6\text{-}12}$), R^2 39.9%, p = 0.0282; race p = 0.0405, ln AUC $_{6\text{-}12}$ p = 0.0687, and 2) Ln MPAG Clr = 13.1896 − 2.2901 (ln age) − 0.5105 (ln AUC $_{6\text{-}12}$), R^2 39.9%, p = 0.0300; ln age p = 0.0434, ln AUC $_{6\text{-}12}$ p = 0.0776. No significant predictors of $AUC_{6\text{-}12}$ or Clr for MPA were found.

Comparison Between Groups Based on Clinical Laboratories

Given the importance of albumin in the regression model for Cl/F and $AUC_{0\text{-}12}$ and the prevalence of increased Ur:Cr in glomerulonephritis patients with reduced serum albumin concentrations, we wanted to explore the differences in PK parameters by distinct clinical groupings. (Table 2) UP:Cr was selected as a clinical variable secondary to the high plasma protein binding characteristics of MPA and MPAG. It is conceivable that highly protein bound drugs may be eliminated in the urine bound to protein in patients with proteinuria and/or they may be preferentially eliminated by metabolism secondary to increased unbound fraction. A cut-point value of 1 g/day was selected based on the premise that UP:Cr less than 1 g/day would be less likely to alter PK. The MPA data shows that Cl/F was significantly increased (790 mL/min vs 305 mL/min, p = 0.0464) and Ctr_{12} and AUC $_{0\text{-}12}$ were both significantly reduced in the high protein excretion group (0.88 mcg/mL vs 5.0 mcg/mL; p = 0.012 and 33.2 mcg h/mL vs 91.9 mcg h/mL; p = 0.018, respectively).

Since MPA and MPAG are highly bound to serum albumin, albumin was also selected for evaluation. (Table 2). Several findings of this analysis were of borderline significance. The MPA Clr was found to be increased nearly 2-fold in the low serum albumin group (p = 0.073). This finding would be expected given that renal clearance would be directly related to Clcr as well as the unbound fraction of MPA. $Cl_{unbound}$ was found to be increased in the low albumin group and this finding was of borderline significance (p = 0.051). Although the renal clearance was enhanced 2-fold, the overall contribution of the kidneys to clearance was low given that only 3% of a MPA dose is normally eliminated unchanged in the urine. [16] MPAG Clr was increased in patients with reduced albumin (p = 0.053), reducing the amount of MPAG available for recycling to MPA and potentially leading to reduced MPA exposure. With regard to MPA AUC values, we found slightly increased MPA AUC $_{0\text{-}12}$ in our high albumin group (p = 0.128), reflecting the reciprocal changes in Cl/F.

The differences in pharmacokinetic variables between age grouping (< 40 years vs ≥ 40 years), race (white vs nonwhite), and gender (female vs male) were also evaluated (data not shown in

Table 2). The MPA MRT was found to be greater in younger patients (21.6 hrs vs 8.23 hrs; p=0.066), but this did not result in a significant p value. Additionally, the MPAG Clr $_{0-12}$ was found to be increased 6-fold in females as opposed to males (66.5 mL/min vs 10.7 mL/min; p 0.047). The Clcr, however, was only ~21% greater in females than males.

Discussion

Our study is the first published report that has focused on describing the pharmacokinetic disposition of MPA and its metabolite MPAG after chronic therapy in patients with lupus nephritis. Additionally, in order to achieve clinical relevance to our work, we have described relevant patient laboratory data that were found to portend variations in pharmacokinetic disposition. Our multivariate regression assessments for prediction of Cl/F and AUC_{0-12} implicated serum albumin and Clcr as the main contributors. Although there is some degree of correlation between serum albumin and UP:Cr, there is also a fair amount of variability between the two measures in individual patients. The combined, correlative contribution of UP:Cr and serum albumin cannot, however be fully evaluated. Hence, it is prudent to assess both the serum albumin and UP:Cr when evaluating initial dosing for highly protein bound drugs such as MPA. The multivariate regression assessment of MPAG Clr determined that log AUC_{6-12} was contributing with gender and age also contributing equally, although in a separate fashion.

The resulting MPA PK parameters for patients with lupus nephritis appear to be comparable with that what has been reported for renal transplant recipients, with the exception of Cl/F, which is up to 2 -fold greater in the lupus nephritis population. Reasons for enhanced Cl/F include increased systemic metabolism secondary to either up-regulated glucuronidation (single nucleotide polymorphisms in the UGT1A9 promoter or steroids), increased MPA unbound fraction (available for hepatic extraction/metabolism), or enhanced renal excretion. Regarding glucocorticoids, patients receiving concurrent steroids had similar Cl/F estimates as patients who were not receiving steroids. Also, steroid dose did not contribute to the Cl/F in the regression analysis. We are currently evaluating the contribution of genotype as a factor in altering MPA clearance. The unbound fraction, implicated as a variable leading to increased drug availability for metabolism is important in our patients given that 40% had albumin concentrations that were < 4 g/dL. The regression analysis for Cl/F implicated serum albumin as a predictive variable.

Enhanced renal clearance could occur secondary to increased free drug available or due to loss of protein bound MPA with the urinary protein, both cases resulting in an increase in Cl/F. However, when we evaluated Clr between patients with UP:Cr < 1 g/day and those with UP:Cr ≥ 1 g/day, the Clr results were similar. It is plausible that the magnitude of difference in Clr was under-appreciated based on our selected cut-point for UP:Cr of 1 g/day. Further review of our data shows a confounding effect of serum albumin levels; while 29% of our UP:Cr < 1 g/day had low albumin levels, 75% of our UP:Cr ≥ 1 g/day had low albumin levels. A previous study of 16 autoimmune disease patients (containing six lupus erythematosis patients) who received 1 g MPA every 12 hours reported a mean MPA AUC $_{0-12}$ of 70.6 ± 28.7 mg h/L, which was comparable to our study. [17] However, it is not clear whether the previous study normalized AUC data to weight or body size to enable appropriate assessments. The MPAG AUC $_{0-24}$ (2017.2 ± 1124) was 2-fold higher than what would have been predicted in our study based on extrapolation of the AUC $_{0-12}$ data. MPAG is minimally active pharmacologically and it is important in enterohepatic recycling and MPA exposure. While it was expected that Clcr would predict the MPAG Clr secondary to MPAG being a polar metabolite that is primarily excreted by the kidneys, our distribution of kidney function did not encompass late stage CKD patients to enable a display of these relationships. Previous clearance data from renal transplant patients has shown MPAG plasma clearance to be highly correlated (R^2 0.86) with glomerular

filtration rate (Clcr) and the mean Clr values for MPAG in patients with mild, moderate and severe kidney disease were reported as 21.7, 10.0, and 5.0 mL/min, respectively. [18] Hence, a patient with severe kidney disease could have a 4-fold reduction in MPAG clearance, resulting in an increase in MPA AUC through recycling. Our regression model suggested that log $AUC_{6\text{-}12}$ along with log age and gender were predictors for MPAG Clr. An increase in recycling AUC predicted a reduction in Clr of MPAG since less drug would be available as the polar, renally excreted metabolite. An increase in age predicted a decrease in MPAG Clr, which would support (indirectly) a role of Clcr. Most of our patients spanned the second to the fourth decade and thus the effects of age on Clcr were not appreciated. Refinements and validation of our model will require addition of representative patients with more severe reductions in Clcr to fully understand the role of renal function.

A study in renal transplant recipients used a multivariate analysis and demonstrated that 24% of the MPA Cl/F could be explained by proteinuria (yes/no), Clcr, and diabetes mellitus. [19] Our data showed that 51% of MPA Cl/F could be explained by serum albumin and Clcr, two readily measured clinical laboratories. The contribution of Clcr to MPA Cl/F was unexpected given the low percentage of MPA (1-3%) that is normally excreted by the kidneys. However, patients with diminished Clcr have been documented to exhibit decreased hepatic metabolism postulated to be due to the CKD state itself or the effect of CKD on the accumulation of endogenous substrates. [20] In subjects with both decreased albumin and decreased Clcr, the AUC lowering effect of reduced albumin (more drug available for metabolism) may be balanced by an increased AUC effect secondary to a reduced Clcr. [21-22] Along another pathway, states of inflammation can have variable effects on drug metabolizing enzymes and transporters. [23-24]

Regression models for a quantitative prediction of the Cl/F based on the serum albumin and Clcr, when validated, could be used to guide dosage regimens. For example, in our current model, for each 20 mL/min decrease Clcr, one would expect a decrease in Cl/F of about 30 mL/min assuming a stable serum albumin of 4.4 g/dL and an increase of about 180 mL/min assuming a concomitant reduction in the serum albumin to 2.9 g/dL. Hence, the effects of moderate reductions in serum albumin would have fairly significant effects on increasing Cl/F versus moderate reductions in Clcr. Since increases in proteinuria often result in concomitant reductions in serum albumin, the combined contributions could enhance the Cl/F of MPA even further. However, more patients with significant proteinuria are needed to provide a more definitive conclusion regarding the contribution of proteinuria to Cl/F for MPA. Although requiring additional validation, the regression equation for $AUC_{0\text{-}12}$ could enable calculations of dosage modifications depending on the targeted $AUC_{0\text{-}12}$ with the assumption of linearity within the clinically obtained plasma concentrations.

While we report the contribution of serum albumin and Clcr (via Clcr) to MPA clearance, there are some limitations to our research. As noted previously, our patients had relatively preserved Clcr, with only three patients presenting with more severe kidney disease (stages 2 and 3). The full contribution of reductions in Clcr to alterations in clearance would require assessment across the spectrum of kidney disease. Similarly, since only two patients in our dataset were nephrotic (UP:Cr > 3.5 g/d), the full contribution of UP:Cr to clearance may actually be under-recognized based on our data with less significant degrees of proteinuria. Additionally, the combined role of albumin and urinary protein to elimination of highly bound drugs in patients with glomerular diseases requires rigorous assessments. Future analyses of our data include assessment of the contribution of genotype for drug metabolizing enzymes and transporters to drug clearance and outcomes and analysis of the contribution of Ctr and AUC to patient outcomes. We hope to better define appropriate concentration or exposure targets for lupus nephritis patients.

Conclusions

MPA therapy in lupus nephritis patients, as opposed to use in renal transplantation is further complicated by urinary protein excretion and hypoalbuminemia, in addition to altered Clcr. Serum albumin and Clcr appear to be the primary contributors to clearance estimates of MPA and should be accounted for when dosing MPA. Similarly, clinical changes that are associated with either response to therapy or progression of disease may necessitate future adjustments to therapy to maintain efficacy and/or reduce toxicity. MPA therapy individualization is possible in lupus nephritis and the results of such interventions require prospective assessments. The acceptable AUC target for MPA therapy will need to be defined specifically for patients with lupus nephritis to enhance clinical outcomes.

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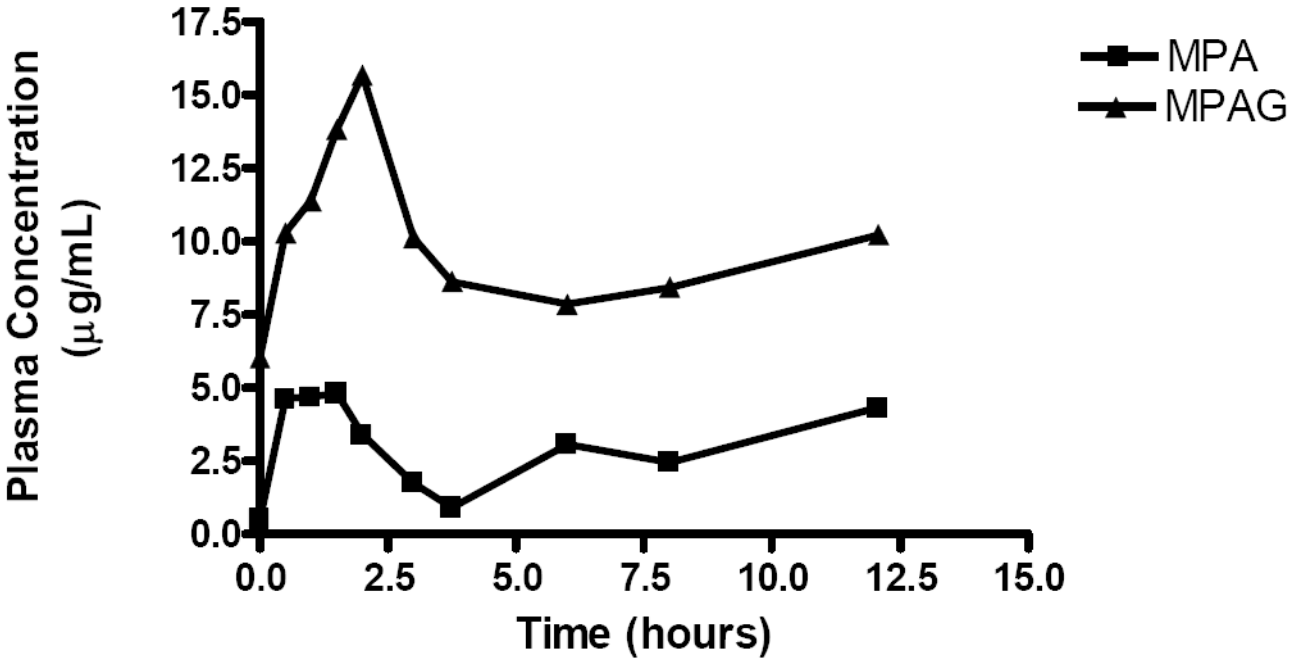

Figure 1.
Figure 1 shows a representative plasma concentration versus time profile for mycophenolic acid (MPA) and its glucuronide metabolite (MPAG) over a 12 hour dosing interval.

Table 1

Pharmacokinetic Parameters in Patients with Lupus Nephritis

Mycophenolic Acid Parameters	
Tmax (hrs)	1.69 ± 1.86
Cmax (mcg/mL)*	21.0 ± 16.2
Ctr_{12} (mcg/mL)*	4.06 ± 5.15
Lambda (hr^{-1})	0.11 ± 0.07
MRT (hrs)	16.3 ± 19.9
AUC_{MPA} 0-12 (mg hr/L)#	78.8 ± 74.1
AUC_{MPA} 6-12 (mg hr/L)#	33.2 ± 39.0
MPA Cl/F (mL/min)+	343 ± 200
MPA Clr 0-12 (mL/min)+	1.85 ± 1.42
Ae 0-12 (mg)	4.81 ± 3.34
Ae 12-24 (mg)	6.53 ± 9.10
MPA free (%)	2.56 ± 1.97
Mycophenolic Acid Glucuronide Parameters	
Tmax (hrs)	3.36 ± 3.56
Cmax (mcg/mL)*	55.1 ± 42.7
Ctr_{12} (mcg/mL)*	28.2 ± 25.2
Lambda (hr^{-1})	0.08 ± 0.05
AUC_{MPAG} 0-12 (mg hr/L)#	518 ± 460
MPAG:MPA	7.09 ± 4.76
MPAG Clr 0-12 (mL/min)+	53.5 ± 52.3
Ae 0-12 (mg)	656 ± 310
Ae 12-24 (mg)	441 ± 341
MPAG free %	9.30 ± 5.23
Free Mycophenolic Acid Parameters	
Cmax (mcg/mL)*	0.44 ± 0.54
Ctr_{12} (mcg/mL)*	0.10 ± 0.15
Ctr_{24} (mcg/mL)*	0.13 ± 0.25
AUC_{MPA} 0-12 (mg hr/L)#	1.76 ± 2.60
MPA Cl/F (L/min)+	27.4 ± 30.5

*normalized to a 1000 mg dose

+scaled to a body size of 70 kg using 0.75 power

#dose-normalized to 1000 mg and weight normalized to 70 kg

Table 2

Clinical Grouping of Patients and Pharmacokinetics

PK Parameter	Mean (SD)		P-value
	UP:Cr < 1 g/day	*UP:Cr ≥ 1 g/day*	
	(n = 14)	*(n = 4)*	
MPA % Unbound	2.09 (1.64)	4.10 (2.42)	0.2017
MPA Ctr_{12} (mcg/mL)	4.97 (5.53)	0.88 (0.22)	0.0118
MPA AUC_{0-12} (mg hr/L)	91.9 (79.6)	33.2 (9.87)	0.0176
MPA Cl/F (mL/min)	305 (146)	790 (423)	0.0464
MPA Clr_{0-12} (mL/min)	1.70 (1.37)	3.35 (2.14)	0.1630
MPA $Cl_{unbound}$ (mL/min)	32695 (40245)	21565 (5982)	0.6235
MPA MRT (hrs)	19.8 (22.4)	6.41 (2.60)	0.0176
MPAG AUC_{0-12} (mg hr/L)	564 (497)	355 (294)	0.4418
MPAG Clr_{0-12} (mL/min)	53.1 (47.8)	68.0 (79.14)	0.6235
Metabolic ratio	6.40 (4.37)	9.52 (6.00)	0.2327
	Albumin < 4 g/dl	*Albumin ≥ 4 g/dl*	
	(n = 7)	*(n = 7)*	
MPA % unbound	2.20 (2.09)	3.35 (2.41)	0.4452
MPA Ctr_{12} (mcg/mL)	4.38 (7.85)	4.26 (3.51)	0.3176
MPA AUC_{0-12} (mg hr/L)	80.4 (112)	85.7 (48.8)	0.1282
MPA Cl/F (mL/min)	522 (408)	342 (238)	0.4557
MPA Clr_{0-12} (mL/min)	2.98 (1.71)	1.46 (1.55)	0.0728
MPAG AUC_{0-12} (mg h/L)	280 (262)	769 (538)	0.0728
MPA MRT (hrs)	13.9 (4.50)	32.8 (29.9)	0.1061
MPAG Clr_{0-12} (mL/min)	80.7 (61.3)	36.4 (37.8)	0.0530
Metabolic ratio	5.19 (3.44)	9.04 (5.19)	0.3176
MPA $Cl_{unbound}$ (L/min)	36.0 (30.6)	30.7 (51.3)	0.0513